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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/916,709	07/27/2001	Michael D. Doyle	001-1	8247

30080 7590 01/04/2005

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EXAMINER	
SMITH, CAROLYN L	
ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 01/04/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/916,709	DOYLE ET AL.	
	Examiner	Art Unit	
	Carolyn L Smith	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/31/04, 8/5/04, 4/5/04, and 10/31/03*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1 page*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *10/1/03*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendments and remarks, filed 10/31/04, 8/5/04, 4/5/04, and 10/31/03, are acknowledged. Amended claims 2-6 and new claims 7-11 are acknowledged. Applicant states claims 2, 3, and 6 are amended. This is incorrect as claims 2-6 are amended.

Applicant's arguments, filed 10/31/04, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from the previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claims 1-11 are herein under examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 7 (lines 2, 4, 5, 12), 9 (line 4), 10 (line 4), and 11 (lines 2, 4, 5, 12) recite the phrase "characterizing a first biological tissue sample" which does not appear to have adequate written basis in the specification, claims, and/or drawings as originally filed. While the

specification mentions characterizing a tissue sample by cutting the sample into first and second sample section sets (see claim 1), it does not mention characterizing a *first* biological tissue sample. Claims 7 (lines 6-11), 9 (lines 2 and 4), 10 (line 2), and 11 (lines 6-11) recite the terms "sub-samples", "subsample", or "sub-sample" which do not appear to have adequate written basis in the specification, claims, and/or drawings as originally filed. The abstract does mention slices that are microdissected into micro samples; however this differs in scope with the broadly recited sub-samples that could include other types of sample scenarios. Claims 9 (lines 3 and 5) and 10 (line 3) recite the phrases "image pixel" and "image pixels" which do not have adequate written support in the specification, claims, and/or drawings as originally filed. Claim 10 (lines 2-3) recite the phrase "either directly or indirectly, to a specific range of multidimensional image pixels" which does not have written support in the specification, claims, and/or drawings as originally filed. Because the introduction of "characterizing a first biological tissue sample", "sub-samples", "subsample", "sub-sample", "image pixel", "image pixels", and "either directly or indirectly, to a specific range of multidimensional image pixels" do not appear to have adequate written support in the specification, claims, and/or drawings as originally filed, these phrases are considered to be NEW MATTER. Claim 8 is also rejected due to its dependency from claim 7. This rejection is necessitated by amendment.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 8 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 8 recites the limitation "said sample" in line 2. There is insufficient antecedent basis for this limitation in the claim, as it is unclear which sample is being referred to, either the first biological tissue sample or one of the indexed tissue sub-samples. Clarification of this issue via clearer claim wording is requested. This rejection is necessitated by amendment.

Claim Rejections – 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. (e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of claims 1-6 is maintained under 35 U.S.C. 103(a) as being unpatentable over Heppelmann et al. (Journal of Microscopy, Vol. 156, Pt. 2, 1989, pages 163-172) in view of Cole et al. (Nature Genetics supplement, Vol. 21, 1999, pages 38-41), Farr et al. (P/N 5,811,231), and Emmert-Buck et al. (Science, Vol. 274, 1996, pages 998-1001).

This rejection is maintained and reiterated for reasons of record. Due to the multiple NEW MATTER rejections within new claims 7-11, these claims will not be considered in the prior art rejection due to the necessity of removing the NEW MATTER.

Heppelmann et al. describe methods for creating multidimensional morphological reconstruction of biological data characterizing a biological tissue sample by cutting histologically thin sections of tissue in two sets of alternating serial sample sections (page 163, lines 1-12) as stated in claims 1 (lines 1-5), 4 (lines 1-5), and 5 (lines 1-4). Heppelmann et al. describe performing these three dimensional reconstructions with graphical techniques and computer-aided methods (page 163, lines 13-14) featuring a spatial matrix of image data as seen in Figure 4 as stated in claims 1 (lines 6-7), 4 (lines 8-9), and 5 (lines 6-7). Heppelmann et al. describe cutting the second set of sections (for ultrastructural examination) and mounting them on single-slot grids to be further examined (page 164, last paragraph) as stated in claim 1 (lines 8-13). Heppelmann et al. describe the sections were mounted in sequence on grids (page 165, lines 12-14) which is reasonably interpreted to be indexed as it has grids with each individual samples placed in a known location as stated in claims 1, 4 (lines 12-20), and 5 (line 5).

Heppelmann et al. describe histologically-staining the first set of sections and adding a coverslip (page 164, fifth paragraph) which could be used for light microscopy reconstructions (page 163, lines 4-5) as stated in claim 4 (lines 6-7). Heppelmann et al. describe that the second

set of tissue sections are covered with a synthetic membrane which is then further cut (page 164, paragraphs 6 and 7) as stated in claim 4 (lines 10-11).

Heppelmann et al. do not teach using a microarray and biological data analyses type which involve mRNA as elected in the species elections. Heppelmann et al. do not teach linking these data to each indexed tissue sample in the multidimensional morphological matrix. Heppelmann et al. do not analyze tissue with monoclonal antibodies or obtain gene expression data and superimpose them on the multidimensional morphological matrix of image data to display correlating values of data with corresponding locations on the matrix.

Cole et al. describe a model for integrating three dimensional expression data obtained using a microarray involving mRNA analysis (page 38, abstract (lines 5-6) and col. 1 (lines 1-4)). Cole et al. discuss cutting tissue in transverse cross-sections (representing X and Y dimensions) available for microdissection and recutting adjacent serial sections in the Z dimension (page 40, col. 1, lines 7-14) which is used to create a multidimensional morphological spatial matrix of image data as seen in Figure 1. Cole et al. discuss the placement of tissue on slides (page 40, col. 1, lines 11-12) and other newly developed fixation and embedding strategies (page 39, col. 2, lines 15-16). Cole et al. describe methods of preparing microarrays from microdissected cells (page 40, col. 1, lines 19-25 and 37-39). Cole et al. discuss that the above processes allows for the determination of exact physical relationships between morphological data (one set) on which to overlay gene expression data (second set)(page 40, col. 1, lines 14-17 and col. 2, lines 16-24) as stated in claims 1 and 5. Cole et al. describe viewing this information on computers and displaying a data chart in three dimensions (page 40, col. 2, lines 26-38) as

stated in claims 1 and 5. Cole et al. show images of stained tissue sample sections obtained from light microscopy (Figure 1, molecular view) as stated in claim 4.

Farr et al. describe a method of measuring biological data, particularly as gene expression levels from specific organs of animal tissues to characterize and identify cellular and subcellular effects of potential toxins on an animal cell (col. 2, lines 52-62 and col. 6, lines 15-23). Farr et al. describe starting experiments with tissue sample and cell lines (col. 6, lines 15-23). Farr et al. describe the results graphically in Figures 1-11 (col. 31, lines 5-6) which consist of multidimensional (3D) representations of the biological data. As can be seen in the Figures 1-11, each data column is indexed and to a particular set of conditions, such as the expression of an enzyme under control of different promoters in the presence of varying concentrations of a test compound (col. 3, lines 24-67). Each of these particular set of conditions was tested with genetic material bound to a solid support membrane which was placed on a 96-well plate (col. 20, lines 53-67; col. 26, lines 9-11; and col. 29, lines 49-51) which allowed for proper indexing and correlation of each set of test conditions to the resulting graphical representations described above as stated in claims 1, 4, 5, and 6. Farr et al. describe an autoradiograph taped to a 96-well plate holder to align the radioactive dots with the holes of the plate holder so that each well is quantified according it each well position (col. 28, lines 23-27) which is a form of image data. Farr et al. describe correlating the results and creating profiles (col. 28, lines 30-32) as stated in claim 6. Farr et al. describe analyzing assays using antibodies to detect proteins (col. 19, lines 55-67 and col. 20, lines 1-14) with expression levels being regulated by interactions between surface receptors and ligands (col. 4, lines 52-55) as stated in claim 2. Farr et al. describe the method to include detecting levels of mRNA (col. 20, lines 25-67) as stated in claim 3.

Emmert-Buck et al. describe a film or membrane applied to the surface of a tissue section on a glass slide (abstract, lines 3-5). Emmert-Buck et al. describe a laser applied to specific locations the film to procure specifically targeted cells that can then be transferred (abstract, lines 5-9) which suggests incising grid patterns of the tissue and selecting only particular subsections.

Cole et al. state that gene expression microarrays hold great promise in studies of human disease states (abstract, line 1). While some technical issues have yet to be addressed, other precise measurement techniques are at hand to view molecular anatomy of normal cells and their disease counterparts (Cole et al., abstract). Farr et al. state the need for quick, inexpensive and reliable alternatives to toxicity testing in animals (col. 2, lines 11-13) such as using techniques of measuring transcription and translation levels of genes (col. 2, lines 52-62). Farr et al. state the kits and methods of their invention yield rapid and direct information about the nature of a compound's action on mammalian cells (col. 3, lines 12-21). Farr et al. also state that the basic construction of the kits, processes, and products of their invention can be altered to provide other embodiments (col. 32, lines 14-21). Heppelmann et al. state that complex morphological structures cannot be fully appreciated without three-dimensional reconstruction (page 163, lines 15-16). Heppelmann et al. point out that stacking of contoured sections for reconstruction is an old technique that is now aided by graphical methods and computers (page 163, lines 16-21). A skilled artisan in the art would have been motivated to improve the methods of representing biological data via direct comparisons of genetic expression and morphological data as stated by Cole et al. (page 40, col. 2, lines 21-28) in order to precisely identify and characterize biological effects on certain tissues as stated by Farr et al. (abstract, lines 1-12). Therefore, it would have been obvious to one having ordinary skill in the art at the time the invention was made to utilize

improved methods of comparison of multidimensional graphic data expression representation to microscopy data, as stated by Cole et al. (page 40, col. 2, lines 21-28) via three-dimensional histological techniques to increase understanding of complex morphological structures as stated by Heppelmann et al. (page 163, lines 15-16 and page 171, lines 11-13), using simple and precision tissue extraction with laser capture microdissection that minimizes contamination, as stated by Emmert-Buck (abstract and page 998, col. 3, lines 2-6 and 12-15), and displaying the gene expression data in easy-to-read three-dimensional graphs as shown by Farr et al. (such as Figure 1), because these exact and efficient techniques would improve accuracy and visual representation for easy interpretation of correlations between the two types of data available to scientists at the time of the invention.

Thus, Heppelmann et al., in view of Cole et al., Farr et al., and Emmert-Buck et al., motivate the instant invention.

Applicants state the present invention in instant claim 1 involves sub-samples which is found unpersuasive as claim 1 makes not mention of the broad term "sub-samples". Applicants mention a section in the specification that describes one aspect of the invention involving the rasterization process (pages 6, 7, 8, and Figure 2). The arguments regarding differences between the prior art and the rasterization step is found unpersuasive as these particular limitations pointed out by Applicants are not specifically stated in the claims. While the claims must be read in light of the specification, the passage on page 6 (last paragraph) fails to provide a clear and explicit definition of what Applicants are arguing. Instead, this passage suggests one aspect of the present invention. It is well known that one "aspect" (page 6, line 25) is a particular

status or phase in which something appears or *may* be regarded (see Merriam-Webster online dictionary definition), but it is not the only possibility. Therefore, the Examiner is at liberty to examine the rasterization limitations set forth in the claims as broadly and reasonably possible, which may not necessarily include limitations found in the specification passage as pointed out by Applicants. Applicants suggest there is no suggestion or teaching of the claimed rasterization step of claim 1. According to the online Graphics Software Glossary definition, "rasterize" is defined as the process of converting a vector image into a bitmap image. This rasterization step is described in the Heppelmann et al. reference above as performing three-dimensional reconstructions of serial sample sections with graphical techniques and computer-aided methods featuring a spatial matrix of image data. Applicants state the spatial matrix of image data is not a pixel-based or voxel-based image as required by claim 1. This statement is found unpersuasive as claim 1 makes no mention of pixel or voxel-based images. Applicants state that Cole and Emmert-Buck references do not describe particular techniques of analysis across a set of arrayed locations or excise areas in a regular raster array. These statements are found unpersuasive as this is a 35 USC 103(a) rejection so that a single reference need not anticipate all of the limitations, but rather all of the limitations must be described within at least one of the prior art references and there must be adequate motivation to combine the references. Applicants state Emmert-Buck teach away from the invention by teaching that one should use laser microdissection to carefully excise around the contours of specific cells, rather than lasing a regular grid pattern across the section. This statement is found unpersuasive as Emmert-Buck state the laser capture microdissection involves selectively adhering the cells of interest (page 998, col. 2, third paragraph) which demonstrates its accuracy that can include all cells in a region

if desired. Emmert-Buck describe selectively transferring a region of tissue or cell cluster or multiple regions (page 999, col. 1, first paragraph). Again, a single reference does not need to address every limitation in the instant invention, but rather the combined references need to address the limitations collectively as a whole. Applicants state Farr et al. do not correlate data spatially to the sample. This statement is found unpersuasive as Applicants have supplied no reasoning or scientific support to explain why the Farr et al. description of correlating results and creating profiles from the 96 well plate that is quantified according to each well position (spatially) would not be considered a correlation of data spatially to the sample. Applicants conclusory statement that improved visualization techniques are beneficial does not make the claims obvious is found unpersuasive as no support or reasoning was given to suggest such improvements for reasons to combine would be considered improper. Applicants' arguments are considered unpersuasive; consequently the 35 USC 103(a) rejection is maintained.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR §1.6(d)). The Central Fax Center number for official correspondence is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carolyn Smith, whose telephone number is (571) 272-0721. The examiner can normally be reached Monday through Thursday from 8 A.M. to 6:30 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached on (571) 272-0722.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instruments Examiner Tina Plunkett whose telephone number is (571) 272-0549.

Ardin H. Marschel 12/30/04
ARDIN H. MARSCHEL
PRIMARY EXAMINER

December 20, 2004